Patients' Refusal of Surgery Strongly Impairs Breast Cancer Survival

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Objective: To compare patient and tumor characteristics and survival between women who refused and women who accepted surgery for breast cancer.

Summary Background Data: Surgery represents the central component of curative breast cancer treatment, but some women decide not to undergo surgery. Recent studies on the prognosis of non operated breast cancer are nonexistent.

Patients and Methods: This study included all 5339 patients aged < 80 years with nonmetastatic breast cancer recorded at the Geneva Cancer Registry between 1975 and 2000. We consulted the clinical files of all nonoperated women to identify those who refused surgery. Patients who refused surgery were compared with those accepting surgery using logistic regression. The effect of refusal of surgery on breast cancer mortality was evaluated by Cox proportional hazards analysis.

Results: Seventy patients (1.3%) refused surgery. These women were older, more frequently single, and had larger tumors. Overall, 37 (53%) women had no treatment, 25 (36%) hormone-therapy alone, and 8 (11%) other adjuvant treatments alone or in combination. Five-year specific breast cancer survival of women who refused surgery was lower than that of those who accepted (72%, 95% confidence interval, 60%–84% versus 87%, 95% confidence interval, 86%–88%, respectively). After accounting for other prognostic factors including tumor characteristics and stage, women who refused surgery had a 2.1-fold (95% confidence interval, 1.5–3.1) increased risk to die of breast cancer compared with operated women.

Conclusions: Women who refuse surgery for breast cancer have a strongly impaired survival. This information might help patients who are hesitant toward surgery make a better informed decision.

(*Ann Surg* 2005;242: 276–280)

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Supported by a PROSPER Grant (3233-069350) from the Swiss National Science Foundation (to Dr. H.M.V.).

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ISSN: 0003-4932/05/24202-0276
DOI: 10.1097/01.sla.0000171305.31703.84

Breast cancer treatment involves multidisciplinary collaboration. For each individual patient, the treatment proposal is not only adapted to the characteristics of the patient and tumor (ie, age, stage, grade, and receptor status), but also to the patients' preference. To make a well-informed decision, every patient should be aware of both the beneficial and adverse effects of the different treatment options.

Despite the increasing efficacy of radiotherapy, chemotherapy, and hormone therapy, these modalities are still adjuvant treatments and until now, surgery remains the central component of curative treatment of breast cancer.

For professionals, breast surgery is intuitively the best way to treat local disease. However, hard evidence in the form of recent studies on the prognosis of nonoperated breast cancer is nonexistent. For women, however, surgery remains a mutilating intervention, even in case of breast-conserving surgery. Some women choose not to be operated and physicians have only subjective arguments to convince their patients to accept surgery.

The aim of this population-based study was to assess the characteristics of women who decide not to undergo surgery for breast cancer and to estimate the impact of this decision on breast cancer-specific survival.

PATIENTS AND METHODS

We used data from the Geneva cancer registry, which records all incident cancers occurring in the population of the canton (approximately 420,000 inhabitants). The registry collects information from various sources, and is considered accurate, as attested by its very low percentage (<2%) of cases recorded from death certificates only.[1] Every hospital, pathology laboratory, and physician are requested to report all cancer cases. Trained registrars systematically abstract data from medical and laboratory files. Physicians regularly receive questionnaires to secure missing clinical and therapeutic data. Death certificates are consulted systematically.

Recorded data include socio-demographic information, method of discovery, tumor characteristics (coded according to the International Classification of Diseases for Oncology[2]), stage of disease at diagnosis, treatment during the first 6 months after diagnosis, survival status, and cause of death.

The registry regularly assesses survival, taking as reference date the date of confirmation of diagnosis or the date of hospitalization (if it preceded the diagnosis and was related to the disease). In addition to passive follow-up (standard examination of death certificates and hospital records), active follow-up is performed yearly using the files of the Cantonal Population Office (office in charge of the registration of the resident population). Cause of death is taken from clinical records and coded according to the World Health Organization's classification.[3]

We included all patients younger than 80 years with nonmetastatic breast cancer recorded at the Geneva Cancer Registry between 1975 and 2000. We collected additional data from the clinical files of all women who did not undergo surgery to differentiate between those who refused surgery and those who did not have surgery for other reasons. In addition, we recorded the reasons for refusing surgery.

We excluded patients who did not have surgery because of other reasons than refusal ($n = 133$), for example, comorbidity or complete response after neoadjuvant chemotherapy.

Clinical tumor size was classified as T0 (tumor not palpable), T1 (<2 cm), T2 (2–5 cm), T3 (>5cm), T4 (invasion of chest wall/skin and inflammatory carcinoma), and unknown. Lymph node invasion was classified as N0 (no clinical evidence of lymph node metastases), N+ (clinical evidence of lymph node metastases), and unknown. Social class was based on the patient's last occupation or, for unemployed women, that of the spouse. Other variables of interest were age, civil status, period, and method of discovery.

Statistical Analysis

We used a case-control approach to compare the characteristics of women who refused surgery with those of women who accepted surgery: cases were patients who refused surgery and controls all other patients. We generated odds ratios of refusing surgery using unconditional multivariate logistic regression analysis. First, we estimated the effect of each variable of interest in a univariate way to identify factors significantly linked refusal of surgery. To estimate which variables were independently linked to refusal, we adjusted the model on all variables with a significant effect in univariate analysis.

Disease-specific survival was studied by the actuarial method. The risk to die of breast cancer among women who refused surgery compared with women who accepted surgery was evaluated by Cox proportional hazards analysis accounting only for age (age-adjusted effect), and for all factors linked to breast cancer survival (multiadjusted effect). Statistical analyses were performed with SPSS software (SPSS 10 version, Chicago, IL).

RESULTS

Among the 5339 women younger than 80 years and diagnosed with nonmetastatic breast cancer during the study period, 70 (1.3%) decided not to undergo surgery. Sixteen patients (23%) refused because of psychologic problems (mainly depression), 10 (14%) chose to undergo alternative therapy, 6 women (8.5%) chose not to undergo surgery because of other medical problems, 1 (1.4%) woman was too afraid to undergo surgery, 1 (1.4%) considered herself too old (77 years) and 1 (1.4%) woman refused because she did not have medical insurance. The remaining 35 (50%) women unambiguously refused surgery, but their reasons were unclear.

Twenty-five women (36%) were treated with hormone therapy only, 2 (2.8%) were treated with radiotherapy, 2 (2.8%) with chemotherapy, and 4 (5.7%) received combinations of chemotherapy, radiotherapy, and tamoxifen. The majority of the patients ($n = 37$, 53%) did not receive any type of treatment. Fourteen women (20%) who refused surgery had a surgical intervention more than 6 months after diagnosis (median follow-up, 48 months; range, 6–93 months), mostly because of progression of local disease.

Table 1 presents the characteristics of the women who refused surgery and of women who accepted surgery. Women who refused surgery were on average 10 years older (68 years) compared with women who accepted surgery (58 years). They were more often single and they were more frequently treated in the public hospitals. The tendency to refuse surgery was relatively constant during the study period, but during the period 1991 to 1995, patients were somewhat more likely to refuse surgery. The tumors of women who refused surgery were approximately 5 times (multiadjusted odds ratio, 5.3; 95% confidence interval [CI], 2.9–9.8) more likely to be detected fortuitously, for example, during the investigation of another physical condition. They also had more often large T4 tumors, and their clinical lymph node status was more frequently unknown.

Figure 1 shows the disease-specific survival curves of women refusing and women accepting surgery. After 5 years, the disease-specific survival was 72% (95% CI, 60%–84%) for women who refused surgery and 87% (95% CI, 86%–88%) for women who accepted surgery ($P < 0.01$). After 10 years, the disease-specific survival rates were 36% (95% CI, 20%–52%) and 75% (95% CI, 74%–76%), respectively ($P < 0.001$). In the subgroup of women who received radiotherapy, chemotherapy, or hormone therapy (alone or in combination) ($n = 33$), the disease-specific survival rates were 81% (95% CI, 65%–97%) at 5 years and 28% (95% CI, 2%–54%) at 10 years. In the group of patients who did not receive any treatment at all, these percentages were not significantly different: 64% (95% CI, 58%–80%) and 39% (95% CI, 20%–58%), respectively. Among the 14 women who had a surgical intervention more than 6 months after diagnosis, the

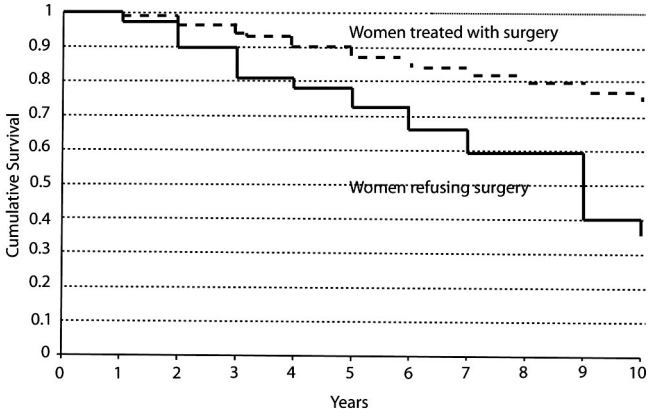
TABLE 1. Comparison of Breast Cancer Patients Who Chose Not to Undergo Surgery and Those Who Accepted Surgery and Factors Linked to Refusal of Surgery

	Refused Surgery (cases, $N = 70$) (%)	Treated With Surgery (controls, $N = 5269$) (%)	Age-Adjusted Odds Ratio*	Multiadjusted Odds Ratio†
Age (yr) (mean)	68	58	1.09 (1.06–1.12)¶	1.08 (1.05–1.11)¶
Civil status				
Single	19 (27)	716 (14)	1	1
Married	20 (29)	3033 (58)	0.3 (0.2–0.6)¶	0.3 (0.2–0.6)¶
Widowed	15 (21)	718 (15)	0.4 (0.2–0.7)‖	0.3 (0.1–0.6)‖
Separated	16 (23)	736 (14)	0.9 (0.5–1.9)	1.1 (0.5–2.1)
Socioeconomic status				
High	4 (9)	495 (16)	1	1
Middle	26 (58)	2075 (65)	1.4 (0.5–4.1)	1.3 (0.4–3.8)
Low	15 (33)	613 (19)	2.2 (0.7–6.9)	2.2 (0.7–7.2)
Unknown	25	2086	—	—
Period of diagnosis				
1975–1980	11 (16)	959 (18)	1	1
1981–1985	12 (17)	865 (16)	1.1 (0.5–2.6)	1.7 (0.7–3.9)
1986–1990	17 (24)	906 (17)	1.7 (0.8–3.7)	1.8 (0.8–4.0)
1991–1995	17 (24)	1122 (21)	1.4 (0.6–3.0)	2.5 (1.1–5.7)§
1996–2000	13 (19)	1417 (27)	0.8 (0.4–1.9)	1.7 (0.7–4.1)
Sector of care				
Private	25 (36)	2620 (50)	1	1
Public	45 (64)	2649 (50)	1.3 (0.8–2.2)	2.3 (1.1–4.6)§
Method of discovery				
Self-examination	4 (6)	753 (14)	1	1
Periodical control‡	6 (8)	1207 (23)	0.6 (0.2–1.6)	0.8 (0.3–2.3)
Fortuitously	21 (30)	384 (7)	3.7 (2.1–6.7)¶	5.3 (2.9–9.8)¶
Symptoms	28 (40)	2669 (51)	0.5 (0.2–1.1)	0.9 (0.3–2.2)
Unknown	11 (16)	256 (5)	—	—
Clinical T				
T0/T1	11 (15)	2063 (40)	1	1
T2	18 (26)	1686 (32)	1.7 (0.8–3.6)	1.8 (0.8–4.0)
T3	4 (6)	230 (4)	2.8 (0.9–9.0)	2.8 (0.8–9.4)
T4	16 (23)	233 (4)	9.4 (4.2–20.7)¶	10.5 (4.4–24.9)¶
Unknown	21 (30)	1057 (20)	3.8 (1.8–8.0)¶	1.8 (0.7–4.3)
Clinical N				
N0	26 (37)	2941 (56)	1	1
N+	21 (30)	1718 (32)	1.4 (0.8–2.5)	0.9 (0.5–1.7)
Unknown	23 (33)	610 (12)	4.5 (2.5–7.9)¶	5.1 (2.4–11.1)¶

*Age-adjusted odds ratio of refusing surgery obtained by unconditional logistic regression analysis.
†Odds ratio of refusing surgery after adjusting for age, civil status, sector of care, period, method of discovery, clinical T, and clinical N.
‡Including clinical breast examination and mammography.
§$P < 0.05$
‖$P < 0.01$.
¶$P < 0.001$.

5- and 10-year disease-specific survival rates were 92% (95% CI, 78%–100%) and 43% (95% CI, 16%–70%), respectively.

The age-adjusted risk to die of breast cancer for women who refused surgery compared with women who accepted surgery was 3-fold increased (hazard ratio, 3.0; 95% CI, 2.1–4.2). After adjusting for period of diagnosis, social class, method of discovery, sector of care, clinical tumor size, clinical lymph node status, and use of nonsurgical therapy



Number of women entering interval

Years	0	1	2	3	4	5	6	7	8	9
Women treated with surgery (n)	5269	5117	4569	4065	3559	3155	2773	2463	2159	1880
women refusing surgery (n)	70	66	57	49	41	35	30	24	20	11

FIGURE 1. Observed breast cancer-specific survival of breast cancer patients who chose not to undergo surgery and those who accepted surgery.

(tamoxifen, radiotherapy, chemotherapy alone or in combination), the risk to die of breast cancer was still 2-fold increased (hazard ratio, 2.1; 95% CI, 1.5–3.1) among women who refused surgery.

DISCUSSION

This study is the first to quantify the impact of patient refusal of surgery on the survival of breast cancer. It clearly demonstrates that women who refuse surgery have a doubled risk to die of breast cancer, regardless of personal factors, tumor characteristics, stage, and nonsurgical treatment.

This study is not randomized and we realize that, even after adjusting for all available variables linked to patient refusal or prognosis, we cannot rule out a selection bias related to unrecorded factors. However, because clinical trials are ethically unfeasible, only observational studies can evaluate the effect of patient refusal of surgery on the outcome of breast cancer.

The importance of surgery for curative treatment of breast cancer was already recognized by the Greek physician Galen of Pergamum (130–200 A.D.).[4] He stated that cancer can only be cured by surgical removal of the tumor where it borders on the healing tissue. Over the past centuries, surgical techniques have evolved enormously and have gone from mutilating amputations of breast, skin, pectoral muscle, and axillary lymph nodes to breast-conserving tumorectomy followed by sentinel lymph node biopsy.[4] Still, surgery for breast cancer is always, to a larger or lesser extent, disfiguring and often affects the woman's body image, self-esteem, and sexuality.[5,6] Nevertheless, 99% of all Geneva women accepted a surgical intervention.

The women who chose not to undergo surgery were quite different from their accepting counterparts. They were older, more often single, and more often treated in the public hospitals. In addition, we observed that women who had their tumors detected fortuitously were at increased risk to refuse a surgical intervention. We cannot conclude whether this is due to the sudden and unprepared confrontation with breast cancer or to the fact that women who do not accept surgery have a tendency to neglect their disease and do not consult a physician when they have symptoms. Anyhow, physicians should be aware that this patient category is at increased risk to refuse surgery and that, for these patients, they may need to emphasize the importance of surgery.

We also observed that women who refused surgery had larger tumors. Again, the design of this study does not allow us to conclude whether this reflects a tendency of women who refuse surgery to neglect their disease or whether large tumor size predisposes to refusing surgery.

There are definitively other factors that affect the decision to undergo surgery or not, which we did not take into account. Siminoff and Fetting investigated factors affecting the decision to undergo adjuvant treatment of breast cancer.[7] They found that the more information regarding the treatment and its side effects was given to the patient, the less likely she was to accept adjuvant treatment. They also saw that the stronger the physician recommended the treatment, the more likely the patient was to accept the proposed therapy. Women who refused adjuvant therapy were more willing to take risks and were generally better educated. In our study, we had no information on educational level, but we observed no significant difference in social class (usually related to level of education) between women refusing or accepting surgery. There was indeed a nonsignificant tendency for the opposite: an increased risk of refusing surgery among women of lower social class.

Most women who refused surgery did not receive any therapy at all. There are only very few studies available on the natural history of breast cancer, ie, the outcome of breast cancer without therapy. Bloom et al studied a series of 250 women with untreated breast cancer (diagnosed between 1805 and 1933) and found particularly poor survival rates: 18% at 5 years and 3.6% at 10 years.[8] Several groups studied the effect of omitting surgery, but using radiotherapy, chemotherapy, and tamoxifen, alone or in combination, on survival of patients with operable breast cancer. Some reported that radiotherapy alone or in combination with chemotherapy is equivalent to breast cancer treatment that includes surgery.[9–13] However, none of these studies included an appro-

priate control group (ie, women treated with surgery), and it is therefore impossible to draw any conclusions on the effect of omitting surgery on breast cancer prognosis. One more recent study looked at the effect of surgery among patients who had a complete response after neoadjuvant chemotherapy.[14] In this selected population, surgery appeared to reduce the local recurrence rate but did not improve survival. However, this study was not randomized, and although some important prognostic characteristics seemed to be well balanced between operated and nonoperated patients, it can not be excluded that "healthier" patients were selected for treatment without surgery.

It is of great importance that women are entirely involved in the decision-making process concerning their treatment, and we acknowledge that they have the full right to choose not to undergo surgery. With the results of this study, physicians will be able to better explain the importance of surgery to patients who are hesitant toward breast surgery. This might help these women make a better informed decision.

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